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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,398	06/30/2003	Mariagrazia Pizza	PP00338.105	1890

27476 7590 02/21/2008

NOVARTIS VACCINES AND DIAGNOSTICS INC.
INTELLECTUAL PROPERTY R338
P.O. BOX 8097
Emeryville, CA 94662-8097

EXAMINER	
GRASER, JENNIFER E	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
02/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/611,398	PIZZA ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 10-25* is/are pending in the application.

4a) Of the above claim(s) *10-18 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,19-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted on 12/5/07 is made. Claims 1-4 and 10-25 are currently pending. Claims 10-18 and 24 were previously withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-4, 19-23 and 25 are currently under examination.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-4,19-21, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Dominighini et al (WO 93'/13202) in light of evidence provided by Pizza (1994).

Dominighini et al disclose the instantly claimed invention directed to a an immunogenic detoxified protein comprising the amino acid sequence of the subunit A of an Escherichia coli heat labile toxin (LT-A, see claims 1-3) the protein having mutations at positions Ser-63-Lys ***and*** Arg-192-Asn and vaccine compositions comprising said protein. Claim 1 of Dominighini specifically recites that position Ser-63 of CT-A or LT-A may be replaced with another amino acid and claim 2 specifically recites at least one additional amino acid specifically including Arg-192 may also be replaced with another

amino acid. Dominighini also teaches that the detoxified protein has a toxicity less than 0.01% of the naturally occurring toxin counterpart, particularly because it is identical to that of the protein instantly claimed. Dominighini et al inherently anticipates the instantly claimed invention as now claimed in light of evidence provided by Pizza (1994) that teach Lys63 causes lose of toxicity (see (Table 1 and 2) and Arg-192-Asn decreases the rate of proteolysis and activation in vivo (see entire reference). Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

Response to Applicant's Arguments:

Applicants argue that Domenighini fails to describe an LT-A having both the amino acid positions corresponding to Ser-63 and Arg-192 replaced with another amino

acid. This has been fully and carefully considered but is not deemed persuasive. As stated in the body of the rejection above, Domenighini et al does teach double mutants and much more. Claim 1 of Dominighini specifically recites that position Ser-63 of CT-A or LT-A may be replaced with another amino acid ***and*** claim 2 specifically recites at least one additional amino acid specifically including Arg-192 may also be replaced with another amino acid, e.g., the same double mutant is included in the scope of the teachings of Domenighini et al. The claims of Dominighini, as well as the teachings of their specification, clearly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domenighini et al, as applied to claims 1-4,19-21, 23 and 25 above, in view of Clements et al (US Pat.6,019,982).

See discussion of Domenighini above. The reference teaches DNA molecules that encode mutant detoxified heat labile toxin of E.coli and mutant detoxified cholera toxin, wherein the mutations are in A-subunit in positions 63 and 192, but differs from the instantly claimed invention by failing to show the codon mutation at position 192 to be a mutation from Arg-192 to Gly- 192. Clements et al show DNA that encodes a mutant detoxified heat labile toxin of E.coli and mutant detoxified cholera toxin, wherein

the mutation at position 192 is mutation from Arg-192 to Gly-192 in an analogous art for the purpose of obtaining a detoxified protein that still evidences adjuvant activity for induction of an enhanced immune response. It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the mutation of Domenighini at position 192 from Asn to Gly as taught by Clements, because Clements and Domenighini et al are both directed to the site directed mutagenesis of heat labile toxin of E.coli at position 192, and Clements et al teaches the advantage of substituting Gly at position 192 as yielding a stable, detoxified, mutant that is devoid of ADP-ribosyl transferase activity, but retains its activity as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192, because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in "no real or potential side-effects, such as diarrhea, associated with its use (see col. 10, lines 5-14). In the absence of a showing of unexpected results, Domenighini et al in view of Clements et al obviate the instantly claimed invention.

Response to Applicant's Arguments:

Applicants argue that Domenighini fails to describe an LT-A having both the amino acid positions corresponding to Ser-63 and Arg-192 replaced with another amino acid. This has been fully and carefully considered but is not deemed persuasive. As stated in the body of the rejection above, Domenighini et al does teach double mutants and much more. Claim 1 of Dominighini specifically recites that position Ser-63 of CT-A

or LT-A may be replaced with another amino acid ***and*** claim 2 specifically recites at least one additional amino acid specifically including Arg-192 may also be replaced with another amino acid, e.g., the same double mutant is included in the scope of the teachings of Domenighini et al. Clements et al show DNA that encodes a mutant detoxified heat labile toxin of E.coli and mutant detoxified cholera toxin, wherein the mutation at position 192 is mutation from Arg-192 to Gly-192 in an analogous art for the purpose of obtaining a detoxified protein that still evidences adjuvant activity for induction of an enhanced immune response. It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the mutation of Domenighini at position 192 from Asn to Gly as taught by Clements, because Clements and Domenighini et al are both directed to the site directed mutagenesis of heat labile toxin of E.coli at position 192, and Clements et al teaches the advantage of substituting Gly at position 192 as yielding a stable, detoxified, mutant that is devoid of ADP-ribosyl transferase activity, but retains its activity as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192, because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in "no real or potential side-effects, such as diarrhea, associated with its use (see col. 10, lines 5-14). In the absence of a showing of unexpected results, Domenighini et al in view of Clements et al obviate the instantly claimed invention.

Applicants further argue that this substitution has no be shown by Clements and Domenighini to not only retain immunogenicity, but also to result in the protein being detoxified and more resistant to trypsin proteolysis than wild-type CT-A or LT-A. The references (Domenighini and Clements) teach the identical mutations. Clements et al does teach the advantage of substituting Gly at position 192 as yielding a stable, ***detoxified***, mutant that is devoid of ADP-ribosyl transferase activity, but ***retains its activity*** as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). Additionally, the proteins would inherently possess the property of being more resistant to trypsin proteolysis. The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192, because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in "no real or potential side-effects, such as diarrhea, associated with its use (see col. 10, lines 5-14). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim Rejections - 35 USC § 112-Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3, 4, 19, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic, detoxified proteins comprising the amino acid of subunit A of an E.coli heat labile toxin (LT-A) wherein the amino acids at positions Ser-63 and Arg-92 of SEQ ID NO:7 are replaced with another amino acid, and further wherein the amino acid at position Ser-63 is replaced with Lys-63 and the amino acid at position Arg-192 is replaced with Asn-192 or Gly-192", does not reasonably provide enablement for immunogenic, detoxified proteins comprising ***any*** amino acid replacement at Arg-192 as instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims recite that a change may be made to position Arg-192 without reciting the substitution which provides for the functional limitations. The specification is not enabled for this broadly claimed invention.

The specification states that substitutions, additions, or deletions, may be made to the defined sequences; however, the specification provides no guidance as to what the amino acids may be changed without causing a detrimental effect to the toxin and with the added features of being immunogenic and protective, e.g., vaccine. It is unpredictable as to which amino acids could be removed and which could be added to position 192. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are

critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key residue could eliminate the function of the polypeptide. It could eliminate its functional properties. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes, as instantly claimed, in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. As stated above, Applicants have not shown the particular substitution and the result it produces, with the exception of Arg-192 to Asn or Gly. Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for

their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. The instant claims allow for substitutions with amino acids of vastly different properties and they do not recite the specific changes in the claims.

Given the lack of guidance contained in the specification regarding acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicant's Arguments:

Applicants argue that since the trypsin cleavage site of LT was well-known at the time of filing, it would be reasonable to expect that the properties of the exemplified Arg192 mutants are shared by other mutants which remove the trypsin recognition sequence. Park et al has been cited to show that the properties of mutations to Ser63 other than those exemplified can be extrapolated to a certain degree. These arguments have been fully and carefully considered but are not deemed persuasive. Applicants have not shown the particular substitution and the result it produces, with the exception of Arg-192 to Asn or Gly. Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of

different amino substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Shanon Foley, can be reached on (571) 272-0898.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

2/9/08

Jennifer Graser
Primary Examiner
Art Unit 1645